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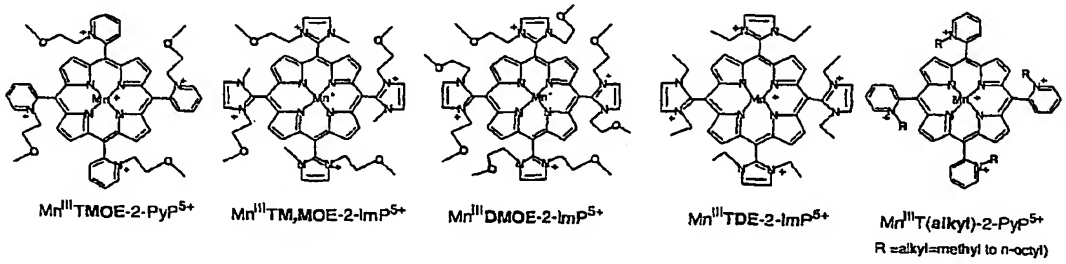
(54) Title: SUBSTITUTED PORPHYRINS



Structures of the Mn(III) porphyrins studied

(57) **Abstract:** To improve bioavailability of the catalytic metalloporphyrin-based SOD mimics Mn(III) 5,10,15,20-tetrakis[*N*-ethylpyridinium-2-yl]porphyrin (MnTE-2-PyP^{5+}) and Mn(III) 5,10,15,20-tetrakis[*N*,*N'*-diethylimidazolium-2-yl]porphyrin (MnTDE-2-ImP^{5+}), three new Mn(III) porphyrins, bearing oxygen atoms within side chains, were synthesized and characterized: Mn(III) 5,10,15,20-tetrakis[*N*-(2-methoxyethyl)pyridinium-2-yl]porphyrin (MnTMOE-2-PyP^{5+}), Mn(III) 5,10,15,20-tetrakis[*N*-methyl-*N'*-(2-methoxyethyl)imidazolium-2-yl]porphyrin (MnTM,MOE-2-ImP^{5+}) and Mn(III) 5,10,15,20-tetrakis[*N*,*N'*-di(2-methoxyethyl)imidazolium-2-yl]porphyrin (MnTDMOE-2-ImP^{5+}). The catalytic rate constants for O_2 dismutation (and the related metal-centered redox potentials vs NHE) for the new compounds are: log k_{cat} = 8.04 ($E_{1/2}$ = +251 mV) for MnTMOE-2-PyP^{5+}, log k_{cat} = 7.98 ($E_{1/2}$ = +356 mV) for MnTM,MOE-2-ImP^{5+} and log k_{cat} = 7.59 ($E_{1/2}$ = +365 mV) for MnTDMOE-2-ImP^{5+}. At 30 μM levels none of the new compounds were toxic, and allowed SOD-deficient *E.coli* to grow nearly as well as wild type. At 3 μM levels, the MnTDMOE-2-ImP^{5+}, bearing an oxygen atom within each of the eight side chains, was the most effective and offered much higher protection than MnTE-2-PyP^{5+}, while MnTDE-2-ImP^{5+} was inefficient. These new porphyrins were compared to Mn(III) *N*-alkylpyridylporphyrins. While longer-chain n-alkyl members of the series exerted toxicity at higher concentration levels, they were very effective at submicromolar levels. Thus, 0.3 μM Mn(III) tetrakis(*N*-n-hexyl-pyridinum-2-yl)porphyrin and its n-octyl analogue offered the same level of protection as did ≥10 μM methyl and ethyl porphyrins. The k_{cat} of methyl and n-octyl porphyrins are identical, but n-octyl is ~10-fold more lipophilic. Therefore, the 30-fold improvement in bioavailability appears to be due to the increase in lipophilicity. MnTDMOE-2-ImP^{5+} and longer-chain Mn(III) *N*-alkylpyridylporphyrins may offer better treatment for oxidative stress injuries than the previously studied MnTE-2-PyP^{5+} and MnTDE-2-ImP^{5+}.

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